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ORIGINAL ARTICLE

Is stereotactic body radiotherapy an alternative to surgery in early stage non small cell lung cancer?

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Summary

Purpose: *To determine local control and overall survival of patients with medically inoperable early-stage non-small cell lung cancer (NSCLC) treated with stereotactic ablative radiotherapy.*

Methods: *Included were a total of 52 patients (7;13% females and 45;87% males) with medically inoperable early-stage NSCLC and who were treated with stereotactic ablative body radiotherapy (SBRT) by a CyberKnife robotic radiotherapy machine between 2009 and 2017. Depending on tumor size and location, median 45 Gy (30-60) were delivered in median 3 fractions (3-5) to Planning Target Volume. As regards the tumor-tracking system; X-Sight lung tracking system was used in 43 (83%) patients, gold fiducials in 4 (8%) patients, and X-Sight spine tracking system in 5 (9%) patients.*

Results: *The median age of patients was 67 years (54–86). Tumor was staged as cT1 in 38 (73%) patients and cT2 in 14 (27%) patients. Median follow up was found to be 23 months (10–84 months). Median survival time was 38 months and, 1-3-5 year survival rates were respectively 94%-53%-33.6%. Locoregional recurrence occurred in 8 (15%) patients and recurrence was local only in 4 (8%) patients, while it was regional only in 3 (6%) and distant only in 12 (23%) patients. During follow up, local, regional and distant recurrence was detected in 27 (52%) cases and median progression free survival was found to be 25 months. 1-3-5 year progression free survival was 71.2%-39%-26%, respectively.*
Grade 3 toxicity was observed in only one patient; no grade 4–5 toxicity was observed.

Conclusion: *A high local control rate with no major toxicity was obtained by SBRT in the patients with medically inoperable early-stage NSCLC. In the near future, SBRT may be an alternative that has growing evidence to support comparable outcomes in selected stage I patients.*

Key words: *stereotactic body radiotherapy, CyberKnife, lung cancer*

Introduction

While surgery is the standard treatment option for early stage lung cancer, some patients can not tolerate resection due to comorbidities. Definitive anatomic resection carries a favorable local control (LC) rate and overall survival (OS) [1]. Patients who are medically inoperable and receiving either no teratment or conventional radiotherapy are significantly less likely to survive than are those who are operated [2]. Local recurrences at the primary tumour site is up to 50% of patients and might be responsible fort this low survival rate [3].

Stereotactic body radiotherapy (SBRT) has been increasingly applied as an emerging modality for the treatment of early-stage non-small cell lung cancer (NSCLC). Using image guidance, SBRT allows for the reduction of dose to critical structures, thus enabling the delivery of much higher doses to the target [4]. The CyberKnife system (Accuray

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Inc, Sunnyvale, CA, USA) integrates a robotically positioned linear accelerator (LINAC) with image-guided stereotactic localization. Its ability to dynamically track targets that move with breathing, with the Synchrony tumor tracking component, is a key feature of this system [5]. Retrospective studies using this system have shown favorable outcomes in LC and OS, of 91% and 75%, respectively [6-9].

In this study, we retrospectively analyzed outcomes of patients with early-stage NSCLC undergoing SBRT in our institution and evaluated factors associated with their outcomes.

Methods

Eligibility

After research ethics board approval was obtained, all patients with a diagnosis of clinically staged IA or IB NSCLC (per the American Joint Committee on Cancer, staging manual, 7th edition) who were treated between 2009 and 2017 with curative-intent radiotherapy were included.

All patients were judged to be unfit to undergo surgery for lung cancer by either a tumor board in our institution comprising a pulmonologist, thoracic surgeons and radiation oncologists, or by referring thoracic surgeons from other medical institutions. Most of our patients (83%) had a histologic diagnosis of NSCLC, and all had available history, physical examination, whole body positron emission tomography (PET) scan, brain magnetic resonance imaging (MRI) or computed tomoghraphy (CT). Lung cancer stage was classified based on the tumour, node, metastasis (TNM) 7.th edition by American Joint Committee on Cancer. The exclusion criteria included recurrent lung cancers or lung metastases, metachronous lung cancer, loss to follow up, or postoperative radiation regimens.

Local responses to treatment were classified according to the modifications of the Response Evaluation Criteria in Solid Tumours (RECIST). Acute and late toxicities associated with treatments were evaluated by the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 [11,12].

Radiotherapy technique and specificationts

From 2009 to 2017 SBRT was performed using CyberKnife (Accuracy Inc., Sunnyvale, CA, USA) radiosurgery system with 6-MV X-rays under respiratory gating. Gating system consists of an infrared tracking mechanism and X-ray imaging device. Internal fiducial markers implantation is generally essential for CyberKnife treatment. Three image guidance systems onboard the Cyberknife platform were used: the XSight Spine Tracking System, which relies on bony anatomy of the spine to locate and track tumors; the Synchrony Respiratory Motion Tracking System, which continuously synchro-

Figure 1. Stereotactic body radiotherapy treatment planning in a single patient.

nizes beam delivery with the motion of the target resulting from respiration by using internal fiducial markers as a surrogate to track tumor motion; and the XSight Lung Tracking System, which tracks the soft tissue (tumor) target with respiration without the need for fiducial markers [10]. The correlation of motion between the external infrared emitters and internal fiducial markers are updated periodically during treatment. Immobilization was achieved with vacuum couch in supine position. Simulation CT (GE Healthcare, Waukesha, WI, USA) was performed using 1.25-mm thick slices by administering intravenous contrast material.

Fiducial placement

Most patients received fiducial placement (Gold Fiducial Markers, Best Medical International Inc, Springfield, VA, USA) into the adjacent soft tissue for real-time image guidance, either bronchoscopically or percutaneously: Two to three gold fiducials, 0.8-1 mm in diameter by 3–7 mm in length, were usually placed in a noncollinear arrangement for best translational correction of the radiation beam position. To minimize fiducial migration, a 1-2 week period of time was allowed before simulation was commenced, in order to decrease procedural edema and permit fibrosis and fixation of the fiducials.

For lesions that were adjacent to and did not move independently of the spine in 5 (9% of the patients), spinal tracking (X-Sight™ Spine Prone Tracking System; Accuray Inc), which uses spine bony landmarks, was utilized. As tumor tracking system, X-Sight lung method was used in 43 (83%) patients, and gold markers in 4 (8%) patients. Pretreatment digitally reconstructed radiographs (DRRs) were generated from the CT scans. Three-dimensional target displacements and global rotations of the spinal structures were determined by comparing radiographs with the DRRs. Translations and global rotations were aligned during patient setup and corrected during treatment delivery.

Treatment planning

The primary tumour in the FDG-PET-CT was delineated as gross tumor volume (GTV). GTV was defined as the tumour visible in lung window of the planning CT scan without further margin for the clininal target volüme (CTV). The planning target volume (PTV) was generated by adding a 5 mm margin to CTV. In evaluating the selected treatment plan, factors such as the homogeneity and conformality index were considered. The median PTV in cases was 35,8 cc (12-91,35). Dose and fractionation schedules were chosen depending on size and location of the primary tumour and lung function parameters. (Figure 1).

Endpoints and follow-up

Approximately 3 months after completing SBRT, a follow-up metabolic and radiologic examination was performed to determine the initial response to SBRT. Three patients were followed by a non-contrast CT and the remaining with PET-CT scans. After the initial follow-up period, a chest CT or PET-CT scan was done to evaluate both tumor size and metabolism every 3 to 6 months for 2 years post treatment - after which follow-up was done on an annual basis. Local responses to treatment were classified according to the modifications of the Response Evaluation Criteria in Solid Tumours (RECIST) [11]. Local failure was defined as meeting any one of the following criteria: a) local tumor enlargement greater than 20% of the GTV compared to the treatment planning CT scan; b) evidence of increasing metabolism using PET imaging; or c) development of a new lesion in the involved lobe. Regional failure was defined as a recurrence within a different ipsilateral lobe or any regional lymph node station including the bilateral hilar, mediastinal, scalene, or supraclavicular nodal stations as defined in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition. Distant spread was defined as either radiographic evidence of a malignant pleural or pericardial effusion, pleural-based nodules, contralateral lung nodules, distant solid organ, central nervous system or osseous involvement.

Statistics

Survival time was measured from the date of SBRT to the date of death or lost to follow-up. The Kaplan–Meier method was used in the survival analysis. The log-rank test was used for categorical variables on OS and PFS. The Cox proportional hazards regression model was used to study the effects of continous variables on OS and PFS. PFS was defined as the time from the first day of SBRT treatment to local, regional, or distant failure or last follow-up visit in living patients without evidence of recurrence or progression. A probability level of 0.05 was considered statistically significant. SPSS software, version 17.0.0 was used for the statistical analyses (SPSS Inc., Chicago, III, USA).

Results

Patient and treatment characteristics

Fifty-two patients diagnosed with early stage NSCLC and not suitable for surgery due to medical comorbidities were treated with CyberKnife radiotherapy machine between 2009 and 2017 and were retrospectively evaluated. The median age was 67 years (range 54-86). Of the 52 patients, 45 (87%) were men and 7 (13%) women. The majority (85%) of patients were smokers, and the median KPS for all patients was 80 (60-100). Tumor location was left upper lobe in 12 (23%) patients, left lower lobe in 10 (19%), right upper lobe in 17 (33%), right median lobe in 2 (4%), and right lower lobe in 11 (21%) patients.

Tumor was clinically staged as cT1 in 38 (73%) patients and cT2 in 14 (27%). In 9 cases histopathological evaluation was not done because of patients comorbidities and in these patients the diagnosis was based on imaging only. Histopathological distribution of 43 cases diagnosed histologically was as follows: 12 adenocarcinoma, 20 squamous cell

carcinoma, and 11 NSCLC with no subtyping. An average of 45 Gy (range 30-60) radiotherapy has been delivered in 3 fractions (range 3-5). The total dose was prescribed to the median 86% (range 70-92) isodose volume. The median biological effective dose (BED) 10 used in this study was 112,5 Gy (range 60-180). Only 9 of the 52 patients (17%) received BED10 <100 Gy. Patient and treatment characteristics are summarised in Tables 1 and 2.

Clinical outcomes

The median follow-up duration after SBRT was 23 months (range 10-84). Median survival time was 38 months. Twenty-two of the 52 subjects eventually died. One, 3 and 5-year survival rates were 94%- 53%- 33,6%, respectively. Locoregional recurrence occurred in 8 (15%) patients and recurrence was local only in 4 (8%) patients, while it was regional only in 3 (6%) patients and distant only in 12 (23%) patients. During follow up, local, regional and distant recurrence was detected in 27 (52%) cases and median PFS was 25 months. One, 3, and 5-year PFS was 71.2%-39% and 26%, respectively. These clinical outcomes are shown in Table 3. The OS and PFS curves are summarized in Figures 2 and 3.

Effect of age, performance score, location of tumor, smoking history, histopathology, tumor stage, tumor size, PTV volume, tracking system and radiation dose, BED10 on OS and PFS were assessed, but no statistically significant was detected. Table 4 shows the results of univariate analyses.

Toxicity

Toxicity was assessed immediately after treatment and again after 3 months of follow-up. SBRT was generally well tolerated and all patients completed therapy as planned. Grade 1-2 radiation

Table 1. Patient characteristics

Characteristics	*n (%)*
Sex	
Male	45 (87)
Female	7 (13)
Age, years	
Median (range)	67 (54-86)
Clinical stage	
T1N0	38 (73)
T2N0	14 (27)
Histopathology	
Adenocancer	12 (23)
SCC	20 (39)
NSCLC	11 (21)
No biopsy	9 (7)
Smoker	
Yes	44 (85)
No	8 (15)
KPS	
80-100	11 (21)
60-80	12 (23)
Tumor location	
Left upper lobe	12 (23)
Left lower lobe	10 (19)
Right upper lobe	17 (33)
Right median lobe	2 (4)
Right lower lobe	11 (21)
Maximum diameter, mm	
mean,median (range)	27.2-25.5 (15-50)

SCC: squamous cell carcinoma; NSCLC: non-small cell lung cancer; KPS: Karnofksy performance status

Table 2. Treatment characteristics

Characteristics	*n (%)*
Tumor-tracking system	
X-Sight Lung	43 (83)
Gold Fiducial	4 (8)
X-Sight Spine	5 (9)
PTV (cc)	
Median (range)	35.8 (12-91.35)
SBRT Doses (Gy)	
Median (range)	45 (30-60)
Fractions	
range	3-5
BED10	
<100	9 (17)
≥100	43 (83)
BED10 value	
Median (range)	112.5 (60-180)
Isodose line	
Median (range)	86 (70-92)

PTV: planning target volume; SBRT: stereotactic body radiotherapy; BED: biologic effective dose

Table 3. Clinical outcomes with actuarial rates with median follow up of 23 months

Outcomes	*n (%)*
Median follow up (range in months)	23 (10-84)
Only local control	48/52 (92)
Only regional control	49/52 (94)
Only distant control	40/52 (77)
Any progression	27/52 (52)
Overal survival	30/52 (58)

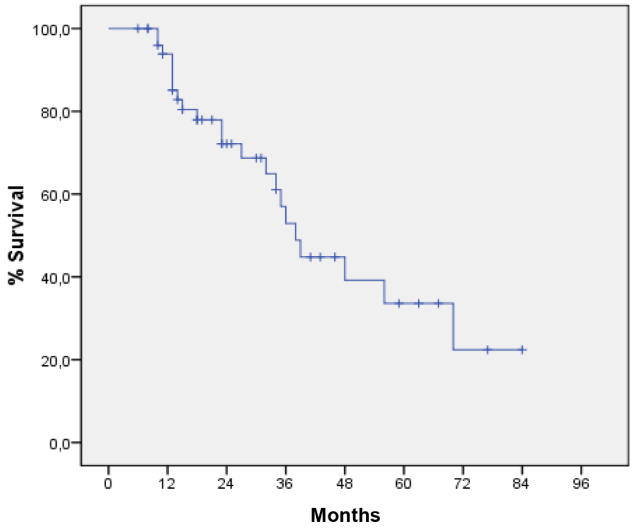

Figure 2. Overall survival of the patients treated with SBRT.

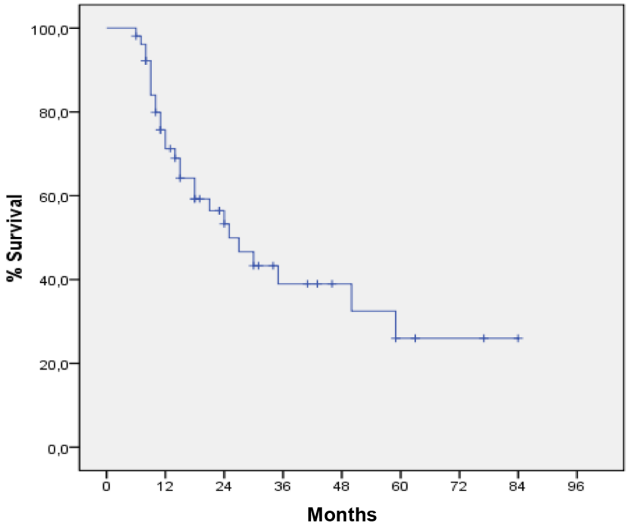

Figure 3. Progression free survival of the patients treated with SBRT.

Table 4. Outcomes of the univariate analyses

Univariate analysis	*p value*	
	PFS	*OS*
Tracking system	0.65	0.61
BED10	0.52	0.95
BED10 category (<100 ->100)	0.82	0.71
Age	0.29	0.26
Smoking year	0.6	0.94
Tumor location	0.95	0.81
Histopathology	0.09	0.11
KPS	0.34	0.3
Tumor diameter	0.2	0.69
Tumor stage (T1-T2)	0.18	0.78
PTV cc	0.34	0.25

BED: biological effective dose; PTV: planning target volume; KPS: Karnofksy performance status

pneumonitis was observed in 6 patients. Grade 3 toxicity was observed in only one patient; no higher toxicity grade was observed. Chest pain was observed in 6 patients. No patient reported rib fracture and hematological toxic effects. Blood routine tests were normal before and after SBRT.

Discussion

Although surgery is the best treatment modality for patients with early stage NSCLC, co-morbid medical problems may restrict surgical procedures in some patients, especially in elderly patients with poor lung function. For early stage patients who are medically inoperable, SBRT is becoming the standard of care [13-15]. The present study described our recent experience with the definitive treatment of early-stage NSCLC inoperable elderly patients, using stereotactic radiosurgery with the CyberKnife system. Series reporting results from conventional radiotherapy for similar patient groups report 2-to 3-year OS rates in the range of 20% to 35%, which are considerably lower than the 53% rate at 3 years reported herein [16].

In medically operable patients refusing surgery a Japanese multi-institutional database with 87 patients showed 5-year survival of 72% and 62% for stage IA and IB, respectively. These figures are considerably better than those obtained in patients with adverse prognostic features who were not considered for surgery. In fact, survival after SBRT might be comparable to that after wedge resection, but adequately powered prospective randomized trials confirming such preliminary observations that might suffer from selection bias are required [17-19].

In recent years, patients have tended to take a more active role in selecting their own treatment, giving consideration to their lifestyles and personal philosophies. In these situations, "shared decision making" plays an important role, which is a process by which clinicians and the patient discuss a treatment strategy for which more than one option is available [20,21]. This approach is applicable to high-risk operable patients with early-stage NSCLC [22]. The demand for SBRT, as a treatment option for high-risk operable patients, is growing. Therefore, it should be considered that both surgery and SBRT are presented as standard treatment options in clinical practice. In order to establish the role of SBRT, radiation oncologists must continue to obtain evidence of the efficacy and safety of SBRT

and to provide patients with detailed information on this treatment option, in cooperation with thoracic surgeons.

Another advantage of SBRT is the low toxicity rates of this treatment modality, and its easy and safe application in experienced centers. Xia et al. [23] reported the toxicities of 43 patients with inoperable stage I/II NSCLC who underwent body gamma-knife radiosurgery prospectively were as follows: both acute grade 2 and grade 3 pneumonitis were 2.3%. Also, He et al. [24] reported the toxicities of 33 patients with stage I lung cancer who underwent image guided stereotactic body radiotherapy via Helical Tomotherapy. In their study, the rate of grade 2 radiation pneumonitis was 21% and grade 2 radiation esophagitis was 30%. Most of these toxicities were observed in central location tumours. In our study, grade 3 toxicity was observed in only one patient and no grade 4-5 toxicity was observed.

The limitations of this study are short follow-up periods, small sample sizes, and its retrospective nature with possible selection bias. Benign lesions or small cell carcinomas might have been included among the 9 cases lacking a histopathological diagnosis.

In summary, we found that SBRT was a feasible and effective treatment modality in patients with early stage NSCLC and medical problems conflicting with definitive surgery. The present results suggest that tolerance of SBRT was acceptable. Further studies will be required to confirm these results in larger populations and with longer follow-up periods.

Conflict of interests

The authors do not report any conflicts of interest. The authors are solely responsible for the content and writing of this manuscript.

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